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Fever of Unknown Origin

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"FEVER OF UNKNOWN ORIGIN" is a well-established phrase in the vocabulary of medicine. It is an expression useful in communication between physicians and, in most instances, categorizes a febrile disorder of obscure etiology. Unfortunately, there is a tendency to regard "F.U.O." as an almost specific diagnostic term. Reflection on the multitude of human afflictions that can be accompanied by elevation of body temperature, however, makes it obvious that "F.U.O." is *not* a clinical entity, and that body temperature is not an appropriate basis for classifications of diseases or diagnostic problems.

The criteria that have been employed in selecting patients in reported studies of fever of obscure origin vary greatly. Some authors have taken a minimum period of 2-3 weeks of fever without diagnosis as a requirement (32, 43) and others have excluded patients with chills (46). Despite these variables in the literature, certain generalizations are possible. In many cases of obscure fever, etiology is never established. Some patients with prolonged fevers survive and live for many years; others die and the cause of fever may remain obscure despite

autopsy examination. The diseases most likely to present as "F.U.O." are infections, neoplasms, hematologic disorders and hypersensitivity states (including the "collagen-vascular" diseases). A febrile illness of obscure etiology is far more likely to be a common disease manifested in an unusual fashion than some rare or exotic affliction (42). For this reason, a knowledge of unusual manifestations and atypical clinical forms of common diseases is most useful in the solution of problems labeled "F.U.O."—as is the case in all differential diagnosis.

The diagnostic technic in a patient with "F.U.O." differs in no essential way from that employed in any patient. Detailed *history*, complete *physical examination*, appropriate *laboratory tests* and careful *observation of the patient's clinical course* constitute the steps in the method. There is no short-cut, no substitute, for these 4 classic procedures. Their fundamental importance has not lessened but has increased with the refinements of biologic and chemical tests, electrophysiologic recording methods, radiologic procedures, biopsy technics and endoscopic examinations.

In the present article, we do not limit discussion to "F.U.O." that remains undiagnosed or to patients in whom the *only* manifestation of illness is fever. Also, we have not hesitated to include fevers of short duration.

In the following pages, several aspects of the clinical significance of fever are covered. Fever is analyzed as a physical sign and certain accompaniments of fever are discussed, selected notes on several diseases in which fever can be prominent and diagnosis difficult are presented and some diagnostic procedures are commented on briefly. Finally, there are appended several brief accounts of illustrative cases.

FEVER AS A PHYSICAL SIGN

Although body temperature is easily measured and is routinely recorded in graphic form in modern hospitals, it is only a physical sign. As a sign, fever can be interpreted properly only in the light of *all* information available to the physician. By itself, it is no more reliable a guide to diagnosis than any other single physical finding such as rales, splenomegaly, pallor, clubbing of the fingers or lymphadenopathy.

Important points in the analysis of fever are *duration, height, diurnal pattern, type of temperature curve,* association

with *chills* or *bradycardia* and the occurrence of *certain complications* of fever itself.

Duration of Fever

Medical practice abounds with brief, prostrating febrile illnesses, without localizing symptoms or signs, which subside spontaneously without specific treatment. These "viral infections" are the most frequent type of "F.U.O." but because of their brief duration are rarely worrisome to the physician.

In general, the longer fever lasts, the more guarded becomes the prognosis and the more important it becomes to determine its etiology. The prognostic implication of long-continued fever is well illustrated by Alt and Barker (1): Of 101 patients discharged from the hospital without diagnosis, 42 of 44 who had fever for less than 10 days had no further difficulty related to the original febrile process, but 26 of 57 patients with fever for longer periods were subsequently found to have serious disease, usually tuberculosis, rheumatic fever or malignancy.

Low-grade elevation of body temperature persists for years in certain patients. The term "habitual hyperthermia" has been applied to a group, predominantly females, with prolonged "fevers" to 100.5 F. over periods ranging from 1 to 19 years. Persons of this type are frequently neurotic and react to emotional stimuli with slight elevations in body temperature (43). Patients with neurocirculatory asthenia react with a greater temperature rise than normal persons to the administration of fever-producing substances such as epinephrine and typhoid vaccine (24).

Reimann (61, 62) has described a group of patients with episodic fever, often associated with abdominal and thoracic pain, arthralgia or leukopenia. He has termed this symptom-complex "periodic" disease. It is useful to know that such cases occur, but evidence that "periodic" disease is a specific entity is lacking, and to exchange the label "F.U.O." for "periodic disease" seems hardly a solution to the problem. Patients with "periodic" disease have been observed to develop one of the collagen-vascular disorders such as systemic lupus erythematosus. We have seen 2 patients with brief bouts of fever and tender lymphadenopathy in whom "periodic" disease was eventually shown to be Hodgkin's lymphoma.

Prolonged fever can accompany diseases which produce

changes in the skin extensive enough to interfere with the heat-dissipating mechanisms. Victims of hereditary ectodermal dysplasia (in which the sweating mechanism is defective) often run fever in hot weather (73). In addition, patients who have undergone extensive sympathectomy (43), or who are taking atropine or related drugs, can have elevations of temperature with exercise or high environmental temperatures; persons with ichthyosis or exfoliative dermatitis may demonstrate the same phenomenon.

The occurrence of transient fever in persons with extensive sunburn is sometimes attributed to absorption of products of tissue injury. However, interference with heat dissipation from the body surface may play a role in this instance also.

Height of the Fever

In prolonged febrile illnesses, the height of the fever is of prognostic significance. Temperature elevations not exceeding 100.5 F. often persist for years without the appearance of other signs of disease; patients with prolonged temperatures of 101 F. or above are likely to develop eventual signs of serious disease (2, 32).

The heat-regulating mechanisms operating through the peripheral circulation and sweat glands are usually able to cut off febrile temperatures at a level which does not threaten life. This regulatory system is so effective in adults that oral temperatures exceeding 106 F. are rare (17).

Heat stroke is often associated with temperature elevations that exceed 106 F. (20). Hyperthermia is frequent in patients with meningitis, cerebrovascular accidents and viral encephalitis, including poliomyelitis; in some cases, at least, this may be due to injury to the hypothalmus. Marked temperature elevations can occur with tumors of the hypothalmus, after brain surgery or following trauma to the upper cervical spinal cord. Additional causes of fevers exceeding 106 F. include lymphomas, acute yellow atrophy of the liver, thyroid crisis and acute pancreatitis.

Certain infections in adults can be accompanied by high fever; oral temperatures exceeding 105 F. should lead one to suspect an infection by the common gram-negative bacilli (such as pyelonephritis), typhoid, brucellosis, tularemia, tuberculosis, malaria, relapsing fever or leptospirosis.

Some infections are characterized by low-grade fever and a few by no fever at all. The temperature of patients with diphtheria is usually less than 102 F. in contrast to the frequency of higher levels in streptococcal pharyngitis. Cutaneous anthrax and sporotrichosis are characterized by low-grade fever, a feature sometimes helpful in the clinical differentiation of these infections from tularemia or glanders.

Type of Temperature Curve

There is a rhythmic change in body temperature during the day; this variation can amount to as much as 2 degrees in normal persons (3). The lowest point is ordinarily between 2 and 4 A.M.; thereafter, the temperature rises to a peak between 4 and 10 P.M. This pattern is apparently unrelated to activity in that persons who work at night and sleep during the day show no reversal of this gradient (48). When disease elevates body temperature, the normal diurnal variation is usually maintained and "spikes" occur in the evening hours.

There are several "classic" types of fever curve. *Continuous* or *sustained* fever is maintained with little or no variation during the day. This type of fever is frequently associated with central nervous system injury and is characteristic of typhoid, pneumococcal pneumonia, the rickettsioses and psittacosis. In patients with pneumonia, a swinging temperature curve points to an etiologic agent other than the pneumococcus.

Remittent fever shows a variation of 1 degree or more during the day but the temperature does not return to a normal level during the 24 hours. Remittent curves are often observed in patients with brucellosis, and the fever of typhoid is sometimes mildly remittent rather than sustained.

Intermittent or *quotidian fever* is characterized by daily elevations with a return to the normal baseline each day. Wide swings in temperature, either remittent or intermittent, constitute a *hectic* or *septic* fever. Hectic fevers point to pyogenic infection (frequently with abscess formation), tuberculosis, malaria, lymphoma or collagen-vascular disease.

A fever curve showing 2 peaks in 24 hours is called a *double quotidian* curve and classically suggests kala-azar or gonococcal endocarditis (but not gonococcemia alone) (25). Even in these diseases, many patients show this pattern for short periods only. Both infections are now rare in this country, and,

at present, a double quotidian curve is more suggestive of miliary tuberculosis than anything else.

In some hectic fevers, reversal of the normal diurnal gradient may be observed, the highest temperatures occurring in the mornings rather than the evenings. Brooks (12) refers to this pattern as "typhus inversus" and states that it occurs most often in patients with tuberculosis, especially miliary disease. This coincides with our experience in which "typhus inversus" has been noted in 7-8% of patients with pulmonary tuberculosis (37). This pattern is frequent enough in Salmonella bacteremia to suggest this infection (6); we have seen it once in a woman with periarteritis nodosa.

Relapsing or *recurrent* fevers are characterized by a series of short febrile episodes interspersed with periods of one or more days of normal temperature. Several types of relapsing fever deserve special comment. Hodgkin's disease is a notorious cause of prolonged fever which defies diagnosis, especially when the disease is limited to abdominal organs and nodes. The "classic" Pel-Ebstein type or recurrent fever is seen in only 10-15% of cases (11). Relapsing fever can occur in patients with tuberculosis. Bottiger (10) reported a patient with tuberculous spondylitis who had a bout of fever regularly every 4-6 days for 6 years, and another with tuberculous lymphadenitis who had fever every 2-3 days for 16 months. Contrary to classic descriptions of brucellosis in Europe, the temperature course of this disease in the United States is rarely "undulant" but is usually intermittent or mildly remittent (70). Other causes of recurrent fever in the United States are rat-bite fever *(Spirillum minus)*, relapsing fever *(Borrelia)*, chronic meningococcemia and malaria.

A number of viral diseases run a biphasic course, beginning with a few days of fever followed by a period of normal temperature and then a recurrence of fever and illness. The course of poliomyelitis is commonly biphasic. The initial "minor illness" is characterized by headache, fever, malaise, sore throat, nausea, vomiting, diarrhea and restlessness. Most patients recover and remain well after the initial period of illness. However, in some persons, a brief remission is followed by the "major illness" or stage of invasion of the nervous system. In others, particularly those developing bulbar involvement, the prodromal symptoms can be followed directly by the paralytic phase without intervening remission. Other diseases in which a "dromedary" or "saddle back" course occurs are Coxsackie

virus infections, Colorado tick fever, dengue (the biphasic course has been overemphasized in this disease), smallpox, yellow fever, lymphoctyic choriomeningitis, vesicular stomatitis and, occasionally, infectious mononucleosis.

Chills

Shaking chills are common in some diseases and rare in others. It is important to distinguish between the common symptom of "chilliness" or "chilly sensations" and true rigors. Because recurrent chills and sweats can be produced by the administration of antipyretic drugs to febrile patients, and true chills can be of considerable diagnostic aid, it is important to inquire about antipyretic medication in all patients who complain of chills.

True chills are unusual in viral hepatitis; their occurrence in a patient with jaundice points strongly to cholangitis or leptospirosis. Similarly, chills are indicative of bacterial endocarditis instead of rheumatic carditis, and bacterial pneumonia instead of pulmonary infarct or viral pneumonia.

The number of chills is of clinical significance. A single chill is the rule in pneumococcal pneumonia (16) and the occurrence of repeated chills in a patient with pneumonia suggests infection with another organism such as the staphylococcus or Klebsiella. Repeated rigors suggest malaria, intermittent discharge of bacteria into the blood stream, or abscess formation. Chills are frequent in infections of the liver, biliary tract (Charcot's intermittent fever) or kidneys. Rigors in a patient with urinary tract infection indicate pyelonephritis, since chills do not occur with simple cystitis. Although chills clearly point toward bacterial infection, they occur in other diseases, examples being Hodgkin's lymphoma, hypernephroma and hemolytic crises.

Hypothermia and Hypotension

Rapid spontaneous defervescence can result in transient hypothermia and a fall in blood pressure. This is seen after chilling in many types of sepsis, during defervescence after a malarial paroxysm and following subsidence of fever by crisis in pneumococcal pneumonia. The mechanism of the hypotension is not clear but because rapid elimination of body heat

entails parasympathethic activity with vasodilatation and sweating and it is not uncommon to see pupillary constriction, involuntary urination, etc., with profound diaphoresis, it seems likely that the lowered blood pressure involves this autonomic mechanism.

Similarly, the artificial induction of defervescence with aspirin (15, 57), cortisone (40, 75) or even antibiotics (57), can be followed by a period of lowered body temperature and hypotension which may last as long as 48 hours. Usually such patients are not in any distress and the hypotension is not an indication of true "shock." Reactions of this type are particularly common in patients with typhoid who receive aspirin or similar compounds. Dowdle (15) reported 8 patients with this disease who were given antipyretics; 4 developed hypothermia of 95-96 F. within 2 hours with persistence of temperature at these levels for 5-7 hours.

In many severe infections, circulatory collapse can occur, but it is particularly common in bacteremias caused by Gram-negative bacilli (31). This is probably related to the endotoxins elaborated by these organisms but shock can certainly accompany infections produced by bacteria that possess no such toxins.

Fever Blisters

Fever often activates latent herpes simplex infection, resulting in typical "fever blisters." Some fevers are more prone to evoke herpes infection than others (64, 65). The incidence of herpes labialis in patients receiving artificial fever therapy, induced by physical means, is as high as 46% (76). Herpes labialis is common in pneumococcal infections, malaria and the rickettsioses. In meningococcemia, the incidence of herpes is about 10% but in meningococcal meningitis it rises to 70%. Streptococcal infections, especially scarlet fever, are often accompanied by fever blisters. However, herpes labialis is so unusual in atypical pneumonia, typhoid, tuberculosis, smallpox and brucellosis that fever blisters argue against the diagnosis of these diseases (81). The rarity of fever blisters in typhoid fever contrasts with their frequency following the therapeutic use of typhoid vaccine.

Albuminuria

A small amount of albumin is frequently found in the urine of patients with fever. This apparently results directly from the elevation of body temperature because it also occurs in patients treated in the fever cabinet (77).

Sweating

Sweating is the most efficient mechanism for dissipation of body heat, and diseases and drugs that interfere with sweating sometimes lead to elevation of body temperature. Marked sweating is usually prominent in patients with fluctuating fevers. Sweating that seems out of proportion to the amount of fever is seen particularly in patients with tuberculosis, chronic suppurative disease of the lung and neoplasms. Administration of antipyretic drugs to febrile patients may produce or aggravate sweating; this is frequent in certain infections such as typhoid but can also occur in fevers of other etiology. Night sweats tend to occur at the low point of the diurnal gradient at 2 to 4 A.M., and often, but not invariably, indicate a low-grade fever. In contrast to night sweats due to disease, nocturnal perspiration in emotionally disturbed persons usually occurs soon after retiring.

Delirium

Fever can produce enough disturbance in cerebral metabolism to cause delirium. There is no specific level of temperature at which this develops. Factors known to facilitate development of febrile delirium include pre-existing disease of the brain and cerebral damage produced by the fever-producing agent. Young adults with fevers of 105 F. may be perfectly oriented, whereas delirium may appear at much lower levels in elderly patients, patients with cerebral arteriosclerosis, alcoholics or patients given sedatives. Delirium is not uncommon in typhoid, the rickettsioses and psittacosis.

Convulsions

Convulsions may be precipitated by fever, especially in children (49). This may herald the onset of epilepsy or some other disorder of the central nervous system; persons with a family

history of convulsive disorders appear to be more susceptible to this complication of fever in childhood.

Headache

Fever often is accompanied by headache. Both febrile and histamine headaches are primarily due to dilatation and stretching of the large arteries at the base of the brain; increasing the cerebrospinal fluid pressure in the subarachnoid space will reduce the intensity of either type (80).

Certain infections are associated with unusually severe headache. These include psittacosis, the rickettsioses, typhoid, influenza and brucellosis.

Bradycardia

Relative bradycardia is common in typhoid and paratyphoid fevers, tularemia and psittacosis. Disproportionate slowing of the pulse is also sometimes observed in infectious mononucleosis, mumps, dengue, atypical pneumonia and yellow fever (Faget's sign). Impressive pulse-temperature dissociation can occur in patients with acute meningitis, presumably the result of increased intracranial pressure. Relative bradycardia, although its specificity is often overemphasized, can be a useful point in differential diagnosis.

SOME SPECIFIC CAUSES OF "F.U.O."

In this section many diseases that can present as obscure fevers are discussed. No attempt has been made to give complete clinical descriptions; rather a few points that may be helpful in considering each as a possible cause of "F.U.O." have been listed briefly.

Factitious Fever

In any case of perplexing fever, especially in the absence of other signs of disease, the possibility of fraud should be entertained. Patients with factitious elevations of body temperature are often familiar with hospital routine, as evidenced by the frequency of spurious fever among physicians, nurses and members of their families (58). Multiplicity of complaints and paucity of signs are usual but occasionally there is evidence of other factitious disease.

The possibility of spurious fever should be suggested by

failure of the temperature curve to follow the normal diurnal gradient, absence of tachycardia with high spikes of fever, unusual hyperthermia and abrupt defervescence unaccompanied by diaphoresis. Often the fraud is committed by holding the thermometer to a warm object or by rubbing it. Some patients can manipulate a thermometer in the mouth sufficiently to produce temperature elevation, and a few can achieve a similar result by manipulating the thermometer with the anal sphincter. Another refinement includes maintenance of a collection of "preset" thermometers. If spurious fever is suspected, the temperature should be measured on several occasions both orally and rectally, having the attendant hold the rectal thermometer in place. These maneuvers usually suffice to expose the fraud. Factitious fever may be produced by less common means. In one reported case (58), a private duty nurse was recording false elevations of temperature in order to prolong her patient's hospital stay. Fever has also been produced by self-administration of pyrogenic materials.

The management of patients with factitious fever is complex. Usually the fever is merely an expression of a deep-seated psychologic disturbance. While the results of psychiatric therapy are often disappointing, it is certainly easier to deal directly with the patient's problem when the possible complication of obscure febrile disease has been eliminated.

Drug Fever

Fever resulting from administration of drugs is encountered with frequency. When another manifestation of hypersensitivity such as urticaria or arthralgia accompanies the fever, the nature of the reaction is easily recognized. However, when fever is the only manifestation of drug allergy, it can pose a difficult problem. Febrile reactions to drugs that develop in patients with underlying febrile disease are not only hard to recognize but can obscure a therapeutic response. Fever in patients with pneumococcal pneumonia usually subsides promptly following administration of penicillin. In patients convalescing from this disease, recurrence of fever classically indicates some complication such as atelectasis, empyema, meningitis or endocarditis. At the present time, however, recurrence of fever in patients with pneumococcal pneumonia treated with penicillin is far more likely to indicate allergy to the antibiotic than a recurrence of bacterial infection (57). Consequently, in the absence

of definite evidence of another complication, penicillin should be discontinued rather than its dosage being increased or another antibiotic added to the regimen. Such a procedure will often prevent confusion and unnecessary prolongation of the patient's hospitalization.

Certain drugs are especially prone to produce isolated fever. Of the antibiotics in common use, penicillin is the most frequent offender; other drugs often implicated are iodides, barbiturates, quinidine, procaineamide, sulfonamides, thiouracil derivatives, isoniazid and para-amino salicylic acid. In a patient suspected of drug fever, it is best and usually possible to discontinue all drugs. If defervescence occurs, they may be reinstituted one at a time and the offending agent identified although an unpleasant or serious reaction may result. When the causative agent is withdrawn, fever usually subsides within 48 hours, although as long as 5 days may be required in occasional instances. It is not unusual to see patients with fevers attributable to more than one drug. If it is deemed inadvisable to discontinue all medication in a patient suspected of drug fever, the agent most likely to cause fever should be withdrawn first. Some drugs are almost never associated with the production of fever, examples being digitalis and the tetracycline derivatives.

Another form of "drug fever" deserves mention. The intramuscular injection of irritating materials such as sodium amytal or paraldehyde may provoke enough local inflammation to produce fever. The administration of repository penicillin, particularly the benzathine salt, is frequently followed by myositis, fever and elevation of the erythrocyte sedimentation rate. When a single dose of 1.2 million units is injected, about 12% of patients will react with fever lasting up to 72 hours (30). The intramuscular injection of large doses of aqueous penicillin sometimes results in a myositis accompanied by fever. When the intravenous route is substituted, fever subsides promptly. Finally, the not-infrequent occurrence of abscess formation at the sites of injection of penicillin, especially in the buttock, should be mentioned; such infections are produced by resistant bacteria and, until surgical drainage is instituted, they may be puzzling causes of "F.U.O."

Tuberculosis

Although infections as a class are responsible for a smaller proportion of cases of prolonged fever than formerly, tuber-

culosis continues to be a surprisingly frequent cause of "F.U.O." In 1956, tuberculosis was one of the 3 most frequent causes of long-continued fever (60) as it was in Cabot's cases in 1911 (13). Bottiger's survey (10) indicates that tuberculosis is the disease most commonly overlooked in patients with "F.U.O." These observations are not surprising if one considers that the total number of cases of tuberculosis has not declined in proportion to the death rate although the number of new cases discovered annually is falling slowly (18).

Tuberculosis is prevalent in a higher age group than previously. The median age at death in tuberculous patients is presently about 50 as compared to a median of 33 only 30 years ago (44). Miliary tuberculosis is often both unsuspected and undetected in elderly patients at the present time.

Any type of fever curve can be seen in tuberculosis. Patients with minimal tuberculosis often have an unusually low morning temperature which rises above "normal" to the extent of only 0.5 F. during the afternoon or evening (12). In more advanced cases, fever can be hectic or sustained, and occasionally a relapsing pattern is seen (10). Patients with high fevers due to tuberculosis often show a peculiar euphoria and hopefulness of recovery called by older writers "spes phthisica" (12).

Tuberculosis of almost any organ or anatomic site can be a cause of prolonged unexplained fever, but infections of the kidney, serous cavities and genitalia are notorious in this respect.

Obscure fever in members of groups in which the incidence of tuberculosis is high (e.g., Negroes and American Indians) or in patients with other conditions known to predispose to tuberculous infection (cirrhosis, Hodgkin's disease, sarcoidosis, gastrectomy, bronchogenic carcinoma, diabetes mellitus and chronic adrenal steroid therapy) should alert the physician to its possibility.

The tuberculin skin test is positive in most patients with active tuberculosis. However, a negative test by no means rules out the diagnosis of miliary tuberculosis. In a recent series of more than 40 patients of all ages with miliary disease, 15% had no reaction to the intradermal injection of first and second strength PPD (37); while repeated testing with larger amounts of tuberculin would undoubtedly have elicited reactions in many whose tests were negative, it is important to realize that a considerable number of patients with disseminated tuberculosis will fail to react to skin tests done with the usual concentrations of antigen.

Occasionally patients with miliary tuberculosis are found to have pancytopenia or severe neutropenia. In this situation, which has been called "acute tuberculous bacteremia," the alterations in the peripheral blood picture can lead to presumptive diagnoses of aplastic anemia or some other blood dyscrasia and thereby delay the recognition of the true etiology of the patient's disease (23).

Brucellosis

Patients with acute brucellosis often have no localizing symptoms or signs. In the United States, the disease is almost entirely limited to farmers, abattoir workers, veterinarians, dairy employees and persons drinking raw milk. The diagnosis is unlikely in the absence of a history of contact with domestic animals or their products. Leukocytosis is unusual; arthralgias are common but true arthritis is rare; upper respiratory symptoms argue strongly against the diagnosis of brucellosis.

Gram-Negative Bacillary Infections

Salmonella infections can be febrile illnesses lasting from a few days to several weeks. Almost any of the many members of this group can produce a typhoidal illness or gastroenteritis. More important is the septic type of infection, "Salmonella septicemia," most often caused by *S. choleraesuis*. Metastatic abscess formation in various tissues, including bone, is common in this form, and repeated chills with a hectic fever are typical. Salmonella septicemia is frequent in children and in patients with debilitating disease (33). The organism can localize in neoplasms or hematomas (28, 33). The incidence of Salmonella infections is increased in thalassemia, sickle-cell disease (38), leukemia, bartonellosis (63), cirrhosis, viral hepatitis (35), neoplastic disease and after gastric surgery (74).

The colon bacillus, *Escherichia coli*, and related members of the enteric flora can produce fulminating bacteremia in newborn infants and also tend to infect patients with debilitating disease such as carcinomatosis, tuberculosis, diabetes and blood dyscrasias. The biliary and urinary tracts are frequent portals of entry. Patients with advanced hepatic cirrhosis are subject to intermittent bouts of blood-stream invasion by coliform organisms (52, 78). Although it has been assumed that this

represents deficiency in reticuloendothelial clearing of intestinal bacteria that normally "leak" into portal venous blood, there is no evidence to support escape of organisms into the blood of normal persons (67). The frequency of hypotension in gram-negative bacillary infections has already been mentioned. Under the term "placental bacteremia" a syndrome of high fever and vascular collapse in pregnant women has recently been described (72). Following fetal death in utero after attempted abortion, massive infection of the placenta by coliform bacilli can occur. Invasion of maternal blood and tissues usually follows, with resulting prostration and death. Massive antibiotic therapy and, in many cases, evacuation of the uterus or hysterectomy appear to be the important measures in treatment.

The gram-negative bacilli of the *Bacteroides* group deserve mention. Primary infection in the pharynx, lung or female genital tract can give rise to suppurative phlebitis and abscess formation in various sites (53). The clinical characteristics of this type of infection have been well described by Fisher and McKusick (22). Bacteroides and anaerobic streptococci are often associated in mixed infections. Because Bacteroides organisms are strict anaerobes and because they may require several days to grow in culture, they are often overlooked. Several anaerobic blood cultures should be taken in every case of "F.U.O."

Streptococcal Bacteremia

Bacteremia caused by group A beta-hemolytic streptococci usually originates from some easily detected lesion such as cellulitis, but there is no obvious primary focus in about 10% of cases (42). Minor traumatized and infected areas of the skin which are easily overlooked can give rise to transient streptococcal bacteremia. These small lesions often lack evidence of surrounding cellulitis or lymphangitis, and the organisms apparently enter the circulation from small areas of adjacent septic thrombophlebitis. This is analogous to bacteremia in pelvic thrombophlebitis following streptococcal endometritis (8). In any patient with chills, fever, leukocytosis and no localizing signs, meningococcemia and streptococcal bacteremia should be considered. The finding of papular or petechial skin lesions favors the former and dermal trauma with infection the

latter. Appropriate blood cultures, of course, establish the correct diagnosis.

Influenza

True viral influenza begins suddenly, frequently with a chill. Manifestations are nonspecific as is true of nearly all viral respiratory infections and consist of fever, headache, shivering, malaise and myalgia. The febrile period in influenza averages only 72 hours but occasionally lasts 5-7 days. Fever rarely exceeds 103 F. and if it does the elevation is usually maintained for only a few hours (71).

Psittacosis

Although there is a tendency to look on psittacosis as a severe form of viral pneumonia, many patients with this disease have high fever, headache, malaise and relative bradycardia for several days before clinical or roentgenographic signs of pneumonitis are detectable. A history of contact with psittacine birds or poultry is often helpful but the virus is carried by so many avian species that a negative history is by no means conclusive. The appearance of pulmonary infiltration in a patient who has been ill for several days with a "typhoidal" picture should immediately raise the possibilities of psittacosis and tularemia.

Leptospirosis

The typical picture of Weil's disease is easily recognized but other leptospiroses may manifest themselves in a nonspecific way with chills, fever, myalgia and headache (47). Occupational exposure to swine, stagnant water or rats, and the findings of episcleral conjunctival injection, cerebrospinal pleocytosis or urinary abnormalities are frequent in patients with leptospiral fevers ("swineherd's disease," "mud fever," etc.), but in many sporadic cases diagnosis is established retrospectively by serologic tests only.

Infectious Mononucleosis

Infectious mononucleosis often begins as a febrile illness with few localizing signs. Most patients have fever, malaise, lymphad-

enopathy and sore throat initially, but about 20% of serologically proved cases commence with a "typhoidal" syndrome of fever, malaise and headache (36). Chills are not infrequent in infectious mononucleosis. Fever usually lasts less than 2 weeks and rarely persists more than a month. Initial leukopenia is common. Of the many organs that can be affected in this disease, hepatic involvement is almost universal and abnormalities in liver function tests often point to the diagnosis before atypical lymphocytes or heterophile antibodies appear (55). The disease should be considered in any young adult with "F.U.O."

Abscesses

Localized collections of pus can be manifested by high fever in the absence of sufficient local disturbance to call attention to an abscess. Subdiaphragmatic, perinephric, pelvic and perirectal suppurations are notorious in this regard. Leukocytosis above 25,000 should direct attention to the possibility of local suppuration.

Unexplained fever (especially a hectic pattern with frequent chills, with or without leukocytosis) after an abdominal operation suggests subdiaphragmatic abscess. The all-too-common practice of administering "prophylactic" antibiotics postoperatively increases the difficulty of diagnosis. "Attenuated" subphrenic abscess may be relatively dormant for weeks or months (9).

Pelvic abscess in the obese or elderly patient may be difficult to detect.

Perinephric abscess often arises from external rupture of a staphylococcal lesion in the cortex of the kidney; a history or the finding of superficial skin infection such as furunculosis or impetigo is of great importance in suggesting this diagnosis in patients with flank pain and fever.

Perirectal abscess is common in patients with diabetes or monocytic leukemia (69). Omission of rectal examination in a patient in diabetic coma has more than once been responsible for failure to detect the infection responsible for the patient's metabolic derangement.

Bronchiectasis

Bronchiectasis and associated acute pulmonary infection sufficient to produce striking fever can exist in the absence of

definitive changes in the routine roentgenogram of the chest. When productive cough or pleuritic pain is prominent, diagnosis is usually obvious but acute pneumonia in bronchiectasis may produce so little change in the patient's chronic respiratory symptoms that it is difficult to implicate the lung as a source of fever.

Bacterial Endocarditis

It is axiomatic that bacterial endocarditis is to be considered in any patient with fever and valvular heart disease. However, in atypical cases, the diagnosis of infection of the heart valves can be most difficult; a frequent example is the elderly patient who presents with hemiplegia, the result of cerebral embolism, in whom the presence of a cardiac murmur is not accorded great note. Among 113 examples of "F.U.O." described by Reid (60), there were 6 cases of bacterial endocarditis. Of these 6 patients, 3 had no murmurs, 5 were not anemic, 5 had no hematuria and none had embolic lesions or splenomegaly. Particularly in the early stages of the disease, cardiac murmurs may be absent and it is now widely recognized that in 10-20% of cases of endocarditis, blood cultures may be sterile for long periods (21). The great importance of recognizing this infection, of course, lies in its curability. The diagnosis is discussed further under Blood Cultures (p. 27).

Neoplasia

It is well known that fever may be the only manifestation of tumors. Almost any malignancy, regardless of location, can produce fever but a few are more likely to do so than others. Fever is not necessarily a late sign of neoplasm, and necrosis or infection of a tumor is not a prerequisite; small tumors with completely viable parenchyma can produce high fever. Neoplastic fever can be of long duration; Bottiger reported a patient febrile for at least 4 and probably 6 years from gastic sarcoma (10).

The fever of neoplastic disease has no distinguishing characteristic; it can be intermittent, recurrent or sustained. Chills are not unusual.

Hodgkin's disease is always listed as a common cause of fever of unknown origin; leukemias, bone tumors, bone metas-

tases and multiple myeloma are all potentially fever-producing illnesses. The "typical" Pel-Ebstein fever persists a few days to 1 week, and regular afebrile intervals lasting 10-14 days occur between fever peaks. This fever is often resistant to salicylates (11). Most cases show an irregular febrile pattern and fever is often present long before other physical signs of the disease develop (11).

Hypernephroma, pancreatic carcinoma and primary or secondary tumors of the liver are prone to produce fever. Once neoplasm is suspected, confirmation by roentgenography or needle biopsy is sometimes possible, although exploratory operation is often required. Elevation of alkaline phosphatase, progressive obstructive jaundice, peripheral thromboses, unilateral hematuria, and so forth, are all well-known signs pointing to these tumors and require no elaboration. The occasional occurrence of polycythemia with hypernephroma (56) is worth mentioning.

Pleural or pulmonary malignancy can produce clubbing of the fingers. Occasionally, pulmonary osteoarthropathy is manifested mainly by migratory arthralgia and swelling of the joints, leading to confusion with many other diseases (79). In particular, pleural mesotheliomas of the localized type are likely to be accompanied by fever, anemia, arthralgia and elevation of the sedimentation rate. Excision of the tumor is followed by prompt disappearance of these manifestations (14).

Lastly, the frequency with which myxoma of the heart is accompanied by fever, anemia, bouts of arthralgia and embolic phenomena deserves mention because of the resemblance to acute rheumatic fever or bacterial endocarditis (27). Hemodynamic signs such as changing murmurs and postural fainting or hypotension have been emphasized in these patients, but the confusion that can arise from the accompanying fever, anemia and embolization by small fragments of the friable tumor of various organs, including the kidney, has only recently been appreciated and should lead to more frequent clinical recognition of this potentially curable disease.

Collagen-Vascular Diseases

Almost every collection of cases of "F.U.O." includes several of acute rheumatic fever. The presumptive diagnosis is often established in retrospect when the patient develops unequivocal evidence of rheumatic heart disease.

Fever is a striking sign in most "collagen diseases." It is least conspicuous in scleroderma and dermatomyositis, but both may present as febrile illnesses. Rheumatoid arthritis is often accompanied by fever and, in its early stages, frank arthritis may be absent, the patient complaining of vague arthralgia and muscle pains.

In systemic lupus erythematosus, fever occurs in almost 100% of cases, more often than any other sign (34). As a rule, fever is prolonged, frequently intermittent and episodes of hectic fever with peaks of 104 F. or higher are common. Early in the course, fever may be the only sign. Lupus erythematosus is more frequent in females and characteristically pursues an episodic course with eventual involvement of many organs. The initial manifestation of illness may be arthritis, nephritis, pleurisy, pericarditis, thrombocytopenic purpura, aseptic meningitis or hemolytic anemia; the first evidence of disease in some patients is a chronic biologic false positive serologic test for syphilis. A search for L.E. cells is indicated in any patient with prolonged fever of obscure origin.

Polyarteritis Nodosa

This disease occurs more frequently in males than in females and deserves serious consideration when fever, abdominal pain and polymorphonuclear leukocytosis are predominant manifestations. Eosinophilia, hypertension, a history of asthma or the appearance of subcutaneous nodules, nephritis, peripheral neuritis or evidence of visceral infarction are all highly suggestive of this disease.

Temporal or Cranial Arteritis

Fever, severe headache and visual difficulties characterize this disorder, which is confined to patients over 50. There is usually a polymorphonuclear leukocytosis. Palpation of the temporal arteries may reveal tender, nonpulsatile cords, a frequent finding since the inflamed vessels become occluded by thrombosis.

Blood Dyscrasias

Fever is frequent in patients with leukemia, particularly the acute forms, even in the absence of complicating infection. Untreated pernicious anemia may be associated with elevation of

body temperature unrelated to infection, the fever subsiding promptly with institution of vitamin B_{12} therapy (2). Acute hemolytic episodes of many types may be accompanied by fever. Fever may be the initial manifestation of sickle cell anemia; episodic musculoskeletal pain and fever occurring in patients with sickle cell anemia, sickle cell-hemoglobin C disease and other variants are often confused with rheumatic fever and osteomyelitis.

Liver Disease

Patients with cirrhosis of the liver and no evidence of infection may have temperature elevations as high as 101-102 F. (2). As has been mentioned, these patients are susceptible to bacteremia caused by gram-negative enteric bacilli.

Cholangitis and pylephlebitis are characterized by swinging fevers and chills and should be considered when hepatic tenderness or enlargement and leukocytosis are present in patients with a history of recent abdominal surgery or cholelithiasis. Jaundice is not necessarily present if pylephlebitis arises from infection outside the biliary tree and its absence does not rule out this disorder. Ascites is present in many patients with infection of the portal vein.

Amebic abscess of the liver can produce prolonged fever. Patients with this lesion may give no history of amebiasis and even failure to find amebae in the stool does not rule out the diagnosis. In many instances, the diagnosis is confirmed by needle aspiration of typical chocolate pus from the liver or pleural space; amebae are rarely demonstrable in such exudates because the trophozoites reside in the wall of the abscess. In a patient with undiagnosed fever and tender hepatomegaly, a therapeutic trial of emetine or chloroquine may be indicated.

A large proportion of adult patients with viral hepatitis have fever of 100-103 F. before jaundice appears, often accompanied by chilly sensations and, rarely, a frank chill (19, 68). The preicteric phase of hepatitis often begins abruptly, lasts as long as a week, and is characterized by fever, malaise, arthralgias, nausea, anorexia, vomiting, upper abdominal pains and, occasionally, skin rashes; it is often confused with other febrile disorders. Fever persisting longer than 3 weeks should not be ascribed to uncomplicated viral hepatitis.

The frequency of fever with hepatoma and other liver tumors has been mentioned above.

Acute Pancreatitis

Hyperthermia is a surprisingly frequent accompaniment of acute hemorrhagic pancreatitis. In a series of 34 patients with this disease observed by Gann, 9 were found to have fevers exceeding 106 F. (26). In occasional instances, the high temperature can direct attention away from the patient's abdominal symptoms and the diagnosis of pancreatic disease can be delayed.

Heart Failure

Cardiac decompensation alone is not likely to cause a temperature elevation of more than 1 degree (45). More fever than this is indicative of a complication such as bronchopneumonia, pulmonary infarction, coronary thrombosis or thrombophlebitis.

Fever commonly develops 24-48 hours after a myocardial infarction, but does not usually exceed 102 F. orally. Greater elevations of temperature in patients with acute myocardial infarction, in addition to directing attention to the possibility of the usual complications, should alert one to look for acute cholecystitis; acute myocardial infarction and acute cholecystitis not infrequently coexist.

Endocrine Disorders

Hyperthyroidism is often associated with elevations of temperature of 99-100.5 F. (3). Hyperpyrexia of 106-108 F. is an outstanding feature of thyroid crisis; there is associated tachycardia, extreme agitation, profuse sweating, occasional vomiting or diarrhea and death is frequent. Most cases have occurred postoperatively, and thyroid storm can usually be avoided by insisting that no patient undergo thyroidectomy or other surgery until a state of euthyroidism has been reached (59). Thyroid crisis can be precipitated by surgery unrelated to the thyroid gland or by infection, and in any patient who develops hyperpyrexia postoperatively or enters the hospital with extremely high fever, the possibility of underlying thyrotoxicosis deserves consideration.

Patients with adrenal insufficiency are likely to have high fever with minor infections and appear to be unusually sensitive to pyrogenic agents such as typhoid vaccine. Acute thy-

roiditis is occasionally manifested principally by fever for some days before local signs appear.

Central Nervous System

Fever may occur after head trauma or spontaneous intracranial hemorrhage. Hyperpyrexia in such cases indicates poor prognosis. Following operations in the region of the pituitary fossa and third ventricle, serious hyperthermia is not infrequent. Patients undergoing surgical procedures or suffering injury in the region of the upper cervical spinal cord often have high irregular fevers for several days.

Episodic bouts of fever over periods of months or years have been reported in patients after intracranial surgery or severe head injuries.

Heat Stroke

The outstanding manifestations of heat stroke are coma, hot, dry skin, often with purpura, and body temperature which may be as high as 110-112 F. Hot weather of several days' duration leads to the occurrence of this disorder in elderly patients and in acute alcoholics. The prognosis is good if a patient is conscious and temperature is below 107 F. Emergency measures to lower body temperature by tubbing in ice water are indicated. The mortality rate is high (39% in one series of 44 patients) (20).

DIAGNOSTIC CONSIDERATIONS

General

It is obvious that the diagnostic possibilities in a patient with fever are so numerous that there is no single routine or plan of study that can be applied to every case of "F.U.O." In the individual case, the decision as to tests and studies to be carried out must be based on information obtained in the history or physical examination. Past illnesses ranging from proved tuberculosis several years before to an upper respiratory infection during the 2 weeks preceding the onset of the present illness are important. Family history, exposure to birds, wild and domestic animals, contact with other ill persons, ingestion

of drugs, change in bowel habits, occupational exposure to sources of infection or toxic chemicals, and so forth, are all important. Repeated questioning is often rewarding because many patients may be stimulated to recall minor incidents and details of great importance. It is not at all rare for the first real lead as to the etiology of obscure fever to come from the elicitation of some new bit of information on requestioning the patient or his relatives. In many instances, a consultant can "break" a case by simply asking a few pertinent questions.

The seasonal incidence of infection is worth considering. Poliomyelitis, mumps, the exanthemata, leptospirosis, the rickettsioses, tularemia, hemolytic streptococcal infections, influenza and other viral respiratory diseases, and many others show a great tendency to occur in a given area at specific seasons.

The predisposition of patients with certain types of degenerative or metabolic disorders to various tumors and infections has been mentioned previously.

The initial physical examination of a patient with "F.U.O." should encompass a careful search for skin lesions, many of which may be entirely overlooked without careful scrutiny of the entire body surface. The "rose spots" of typhoid may number less than a dozen; the tender papules of meningococcemia can be few; petechiae of the conjunctival sac, the ocular fundi, the nail beds, and so forth, may raise the possibility of endocarditis for the first time. Subcutaneous nodules, enlarged lymph nodes, aneurysmal dilatations of superficial vessels or abdominal, mammary and testicular masses may be detected by systematic palpation. Auscultation of the lungs, heart and abdomen should be carried out in every patient. A tiny patch of rales, a faint murmur or an unexpected bruit or friction rub over a viscus can be the sign that first directs attention to an organ as the possible seat of disease.

It is on the basis of careful consideration of the facts accumulated by these initial procedures that the decision to obtain certain types of bacterial cultures and serologic tests, to perform skin tests, to obtain bone marrow or other tissues by biopsy or to order various roentgenographic examinations must be based.

Continuing search for the development of new physical signs and careful observation of the course of disease as it unfolds, coupled with periodic re-evaluation of the data accumulated in

laboratory and x-ray reports are as essential in the care of patients with prolonged fever as is the execution of the initial examinations.

Blood Cultures

Bacteremia may be more or less continuous as in bacterial endocarditis, the first stage of typhoid and in brucellosis, or it may be transient.

Beeson, Brannon and Warren (4) compared the number of organisms in arterial blood and venous blood obtained from several sites in patients with endocarditis and demonstrated that the bacterial count was remarkably stable over long periods, indicating that organisms were entering the blood at a constant rate and not in irregular spurts and showers.

Transient bacteremia is far more common than continuous bacteremia. Manipulation of infected or contaminated tissues can cause a sudden shower of organisms into the blood stream, often with typical chill and fever. Bacteremia of this type occurs after instrumentation of the genitourinary tract, uterine curettage for septic abortion, tonsillectomy, dental manipulations and after incision of an abscess (8).

In bacterial endocarditis, positive blood cultures are usually obtained with ease or not at all. There are now many excellent studies showing that in patients with suspected endocarditis, 2-4 cultures daily for no more than 5 days is the proper schedule rather than many cultures in a single day (5, 29). To extend attempts at diagnosis beyond this is unsound and the decision as to therapy should not be delayed. In intermittent or transient bacteremia, there is a lag period of about 1 hour between the time of a sudden influx of bacteria into the circulation and the onset of a rigor. In patients with intermittent chills, blood for culture should ideally be obtained during the hour preceding the expected chill or spike in temperature. When diagnosis in a febrile patient is obscure, many cultures at frequent intervals are indicated. Chronic meningococcemia is an example of a disease in which the causative organism may be isolated only after multiple cultures have been made.

The question of the comparative value of arterial versus venous blood cultures is often raised. The evidence indicates that insignificant numbers of bacteria are removed from the blood circulating through an extremity, and therefore blood

from the antecubital veins is as likely to contain organisms as blood from the brachial or femoral arteries (4, 51).

Blood cultures should be collected in both aerobic and anaerobic media, and a few cultures should always be incubated under increased carbon dioxide tension.

The duration of incubation of cultures can be important. Growth is usually detectable after 2 days of incubation. Occasionally, when the number of organisms is small, the organism is slow-growing or when inhibitory substances are present, growth may be delayed and cultures should not be discarded for at least 3 weeks.

Certain bacterial infections are frequently associated with negative blood cultures. These infections lie predominantly in the area drained by the portal venous system and include liver abscess, pylephlebitis, cholecystitis, appendicitis and peritonitis. Libman states that of 15 cases of extensive suppurative pylephlebitis, bacteremia was demonstrable in only 1 (50).

Other Cultures

Bone marrow culture is of value in the diagnosis of disseminated tuberculosis, brucellosis, histoplasmosis and some cases of bacterial endocarditis. Using a special technic, Katz and Lifschutz (41) reported the demonstration of tubercle bacilli in the marrow of 89% of 75 patients with hematogenous tuberculosis. Severe pyelonephritis may exist in the absence of pyuria and, therefore, culture of the urine should be performed whether pyuria is present or not. Quantitative urine cultures are of great aid in interpretation of results; irrespective of the cellular content of the urine, if as many as 1,000 bacteria per ml. of urine can be demonstrated, active infection is probable and with 10-100,000 per ml., it is almost certain (39, 66).

Roentgenograms

Several weeks may be required after hematogenous dissemination of tubercle bacilli before miliary lesions develop to a size visible by roentgenogram, and some patients with miliary disease never develop lesions detectable by x-ray. When hematogenous dissemination of tuberculosis is suspected, the chest x-ray should be repeated at weekly intervals. All patients with prolonged fever should have pyelography.

Biopsy

Lesions characteristic of "collagen-vascular" disease may be observed in almost any tissue. Lymph nodes are often helpful in the diagnosis of lupus erythematosus. Biopsy of apparently insignificant skin lesions often reveals sarcoidosis, a disease which is occasionally associated with high fever. Muscle biopsy may show lesions of leptospirosis, polyarteritis nodosa, dermatomyositis or trichinosis. Biopsy of serous membranes is useful in establishing a definitive diagnosis of tuberculosis or neoplasm of the pleura, pericardium or peritoneum. Any palpable lymph node should be considered for biopsy; inguinal nodes are usually less satisfactory than those from other areas. Marked lymphadenopathy is not necessary because sarcoidosis, lupus, metastatic carcinoma or tuberculosis can be found in nodes that are barely palpable. Biopsy of a scalene node is of usefulness in some patients with pulmonary disease or evidence of mediastinal involvement. Liver, kidney and lung are now accessible to needle biopsy and these tissues can provide information of great value in selected patients.

Sedimentation Rate

The sedimentation rate is often normal in brucellosis and trichinosis.

Serologic Reactions

A generous sample of serum should be collected and stored early in the course of febrile illness. Antibiotic therapy may delay demonstration of a rise in antibody levels. This phenomenon has been clearly demonstrated in psittacosis and the rickettsioses. For example, Meyer and Eddie (54) observed a patient with psittacosis, proved by isolation of virus and treated with tetracycline, in whom a significant rise in complement-fixing antibody did not occur until 6 months after onset of illness.

Histoplasmin, coccidioidin and blastomycin skin tests indicate, as does the tuberculin test, past or present infection with the agent in question. These tests are often negative during active mycotic disease; in some instances, the complement fixation test may be positive when the skin test is negative.

The heterophile test for infectious mononucleosis is nonspe-

cific, in that sheep cell agglutinins occur in the serum of normal persons, in response to injection of horse serum, and occasionally in other conditions. Fortunately, the specificity of the test can be increased by absorbing the serum with guinea pig kidney prior to testing against sheep erythrocytes. Cold agglutinins are active against sheep cells and may be responsible for false-positive heterophile tests if serum is not absorbed or if cold agglutination is not dispelled by warming to 37 C. (36, 55).

Therapeutic Trial

The administration of certain drugs to patients with obscure fever may give information of diagnostic value. Therapeutic trial is not synonomous with administration of antibiotics. Among other drugs with more or less specific actions are antimalarials, antiamebic agents, salicylates, colchicine, arsenicals and perhaps nitrogen mustards and related compounds. The adrenal steroids are so nonspecific in their antipyretic effect and their ameliorating action as to be almost useless in therapeutic trials aimed at establishing a diagnosis.

The beneficial effect of salicylate therapy can be of great assistance in establishing a diagnosis of rheumatic fever. Adequate dosage in a patient with acute rheumatic fever will relieve the joint symptoms within 18-24 hours, and will bring the temperature to normal within 72 hours. Although salicylates will lower fever in many febrile disorders, prompt subsidence of signs and symptoms of inflammation strongly suggests rheumatic fever.

It may be necessary to administer a drug for some time before final decision about a patient's response can be reached. For example, response to proper antibiotic treatment in bacterial endocarditis may require days or weeks, and in typhoid or other Salmonella infections, chloramphenicol takes 3-4 days to produce a response. Finally, it should be recognized that an apparent response to initiation of a drug may be coincidental only and efforts to establish the etiology of the disease should be continued. We have recently seen a patient with Hodgkin's disease whose fever (a classic Pel-Ebstein pattern) "responded" to penicillin no less than 4 times during the 2 months before diagnosis was established by histologic examination of an excised node.

ILLUSTRATIVE CASES

Because diseases as basically unrelated in etiology and pathogenesis as typhoid, hepatoma, polyarteritis nodosa, acute hemorrhagic pancreatitis and heat stroke can produce "F.U.O.," it is difficult to generalize in any really useful fashion about the corresponding multiplicity of clinical problems and diagnostic approaches. The other extreme in considering so broad a subject as fever of obscure etiology is the compilation of a series of detailed reports of cases that have posed diagnostic difficulties. While such a collection may be utilized occasionally as a reference, it is improbable that many will read it through at a sitting and, difficult as generalization may be, it is probably preferable to interminable specific clinical details drawn from the personal experiences of one or a few.

In this section, we have chosen to discuss 11 cases. None is described in great detail. Several presented the problem of "F.U.O."; in others, the diagnosis was established with relative ease but the course of illness or response to therapy demonstrates points which we believe are worthy of emphasis.

Figure 1 shows the clinical course of a patient who was acutely ill as a result of bronchogenic spread of pulmonary tuberculosis. Diagnosis was established quickly by roentgenogram of the chest and sputum examination. The institution of specific chemotherapy was followed by an increase in hectic fever for about 2 weeks, prominent features of which were "typhus inversus," with high morning spikes and, on the 10th day, a double quotidian pattern of the type described in gonococcal endocarditis and kala-azar. Worthy of note are the occurrence of chills as late as 10 days after treatment was begun and the return of the initially low serum sodium to normal at about the time that defervescence began. The apparent exacerbation of fever by chemotherapy in this case has occurred often enough in our experience that we no longer regard continued or increasing fever for 2-3 weeks as an indication of failure when a therapeutic trial of antituberculous drugs is begun in a patient with "F.U.O." (see Fig. 5). Tuberculosis is the commonest cause of reversal of the diurnal temperature gradient and of the "double daily spike" in the United States at the present time.

Figure 2 is the record of pulse and temperature in a malingerer who was demonstrated to have spurious fever. Noteworthy are the failure of heart rate to change with sudden

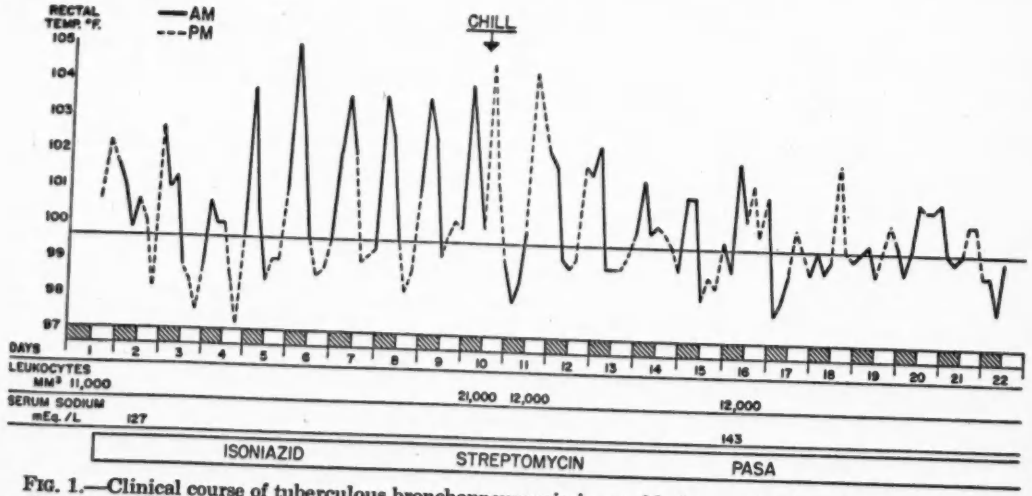

FIG. 1.—Clinical course of tuberculous bronchopneumonia in an elderly man treated with isoniazid, para-aminosalicylic acid and streptomycin.

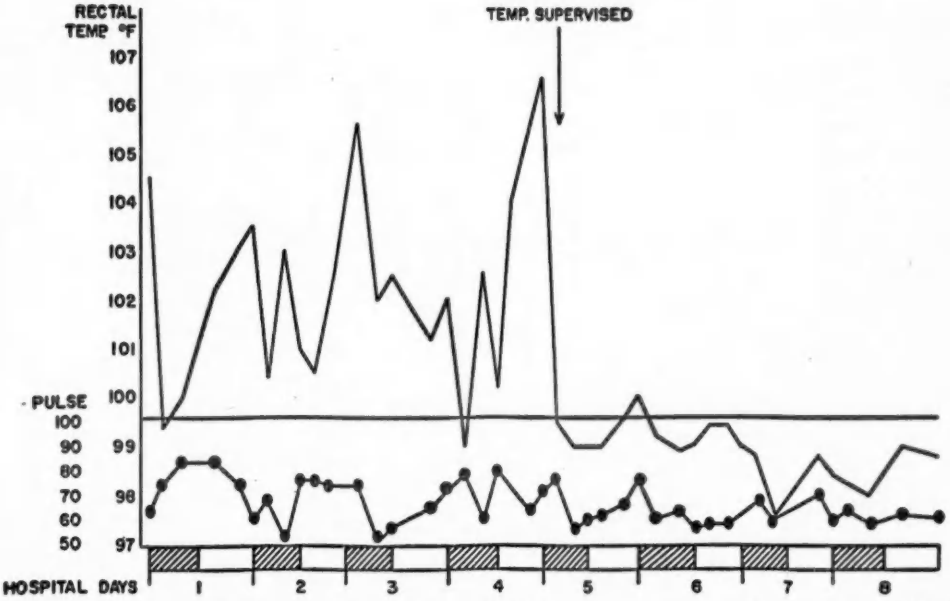

FIG. 2.—Pulse and temperature chart of a patient with factitious fever. (From Yale J. Biol. Med. 26:491, 1954.)

febrile spikes and the occurrence of elevations of temperature at times that vary from the expected pattern of evening rises. These 2 features, coupled with the lack of other objective evidence of illness, led to rapid detection of the fraudulent recordings.

Figure 3 shows a recurrence of fever during the second week of treatment of pneumococcal pneumonia with penicillin. There was no evidence of a bacterial complication and it was decided to stop penicillin on the 10th day. Withdrawal of the drug not

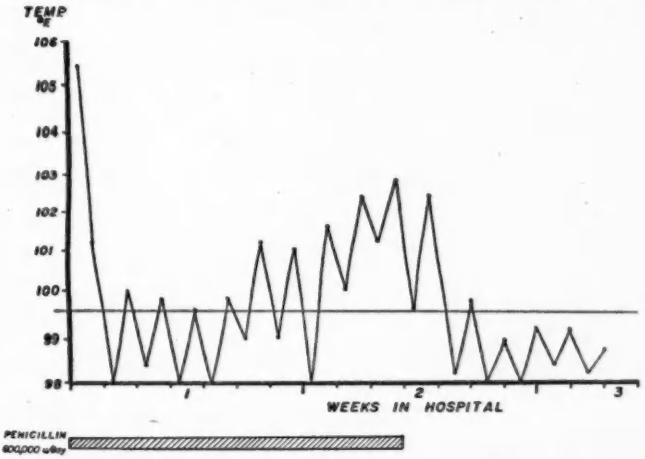

FIG. 3.—Febrile "relapse" produced by hypersensitivity to penicillin in a patient with pneumococcal pneumonia. (From J.M.A. Georgia 45:389, 1956.)

only established the diagnosis of drug fever but was also the definitive therapeutic maneuver. It is not difficult to imagine how different the patient's course might have been if, "just in case," the physician caring for her had increased the dosage of penicillin or had added a "broad-spectrum" drug to the regimen.

Figure 4 depicts 2 bouts of fever in a patient convalescing from surgical repair of an atrial septal defect. Subsidence of fever after withdrawal of quinidine, a drug notorious for inducing isolated fever, was short-lived. The second febrile epi-

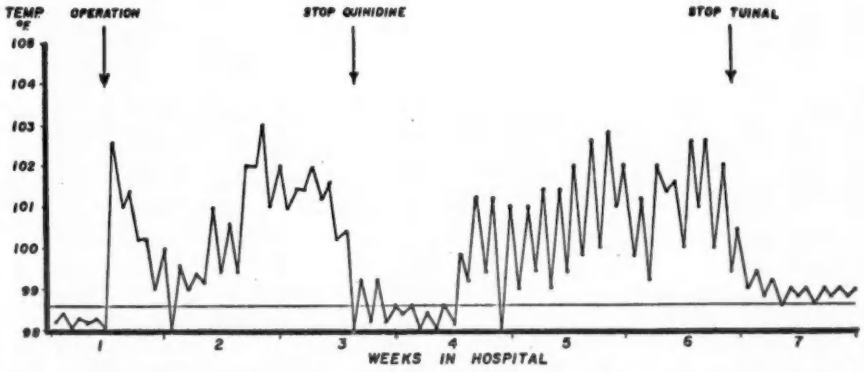

FIG. 4.—Drug fevers produced by quinidine and a barbiturate in a postoperative patient.

sode subsided when the patient's nightly barbiturate was discontinued. Drug fevers prolonged this patient's hospitalization for at least a month.

Figure 5 is an extreme example of the conversion of a sustained fever in a patient with miliary tuberculosis into a swing-

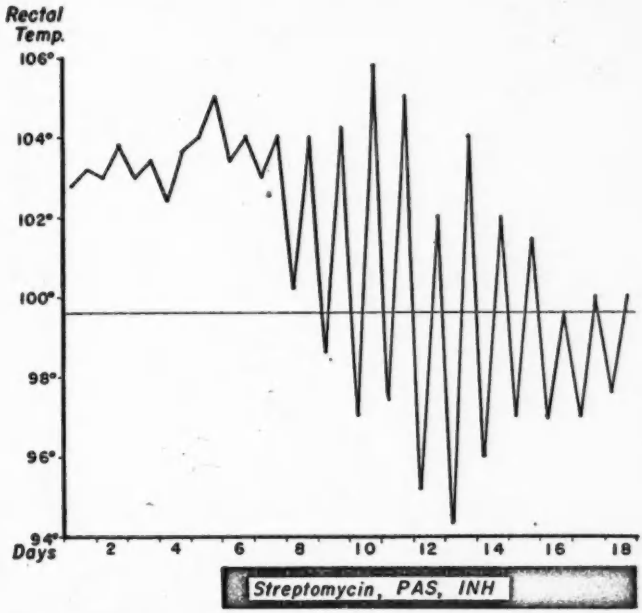

FIG. 5.—Striking hectic fever following initiation of chemotherapy in a patient with miliary tuberculosis.

ing, hectic pattern by chemotherapy. As mentioned above, this is by no means infrequent and, in the absence of other evidence of treatment failure, should not be used as the basis for discontinuing a trial of antituberculous therapy before at least 4 weeks have passed. Many patients with tuberculosis respond to chemotherapy with prompt lessening of fever, and the type of reaction described here is emphasized as occurring in a minority of cases.

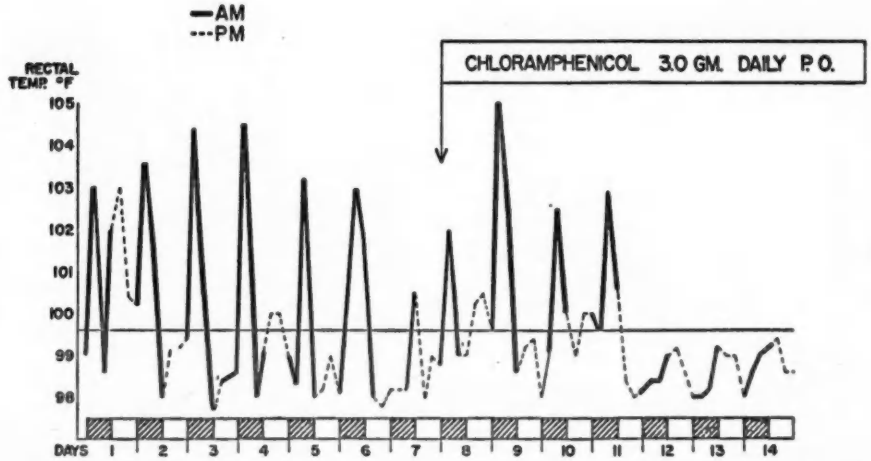

FIG. 6.—Subsidence of fever 3 days after initiation of chloramphenicol therapy in a patient with chronic Salmonella bacteremia complicating hepatic cirrhosis. (From J.M.A. Georgia 45:389, 1956.)

Figure 6 depicts a portion of the course of a patient with hepatic cirrhosis who had intermittent bouts of chills and fever for nearly a year. *Salmonella montevideo* was cultured from blood and bone marrow on several occasions. As shown in the illustration, when chloramphenicol was begun, hectic fever continued for 3 days before a response was evident, similar to the delayed response of typhoid to this drug. There was also a

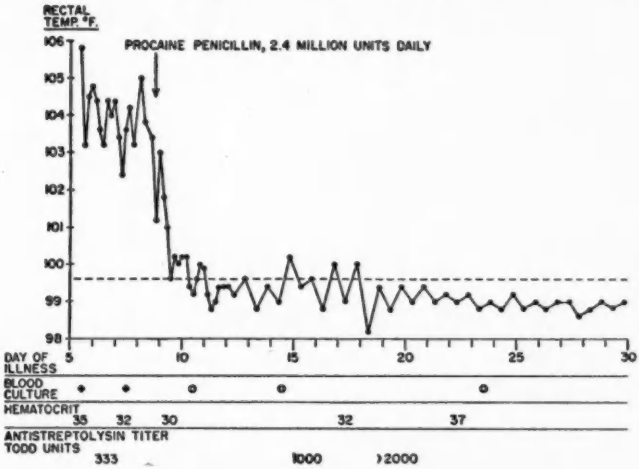

FIG. 7.—Clinical course of group A beta-hemolytic streptococcal bacteremia originating from an inconspicuous infected abrasion of the finger.

striking reversal of the diurnal temperature gradient in this patient who had shaking chills with great regularity at 4 A.M. This pattern, as mentioned, suggests tuberculosis, but we have also seen it on a number of other occasions in Salmonella bacteremias.

Figure 7 is the clinical course of acute beta-hemolytic streptococcal bacteremia originating from a small infected abrasion of a finger. Chills, fever and leukocytosis should always lead to a careful search for such a focus. In one recent period of 3 months, we have seen 4 such cases, all having their etiology in insignificant superficial lesions of the extremities.

Figure 8 shows the course of fever in an elderly woman who

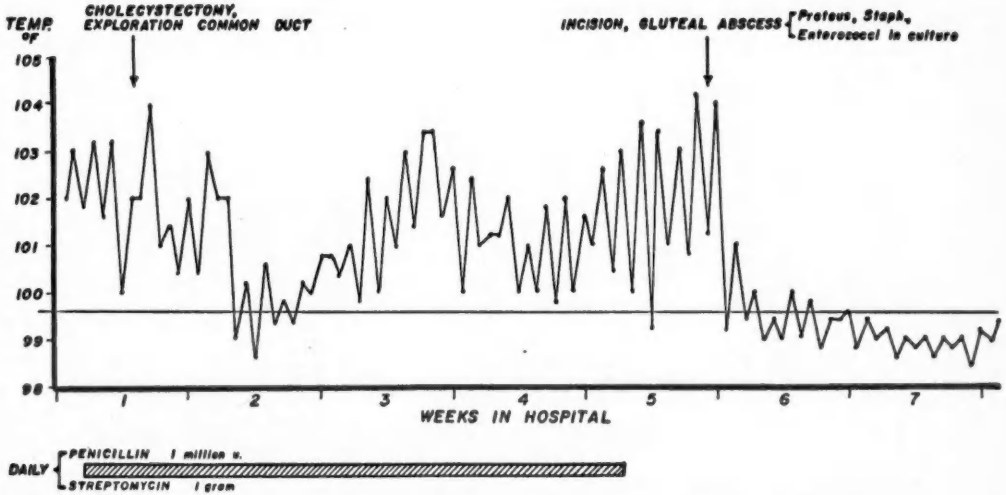

FIG. 8.—Postoperative fever in an elderly female, finally traced to infection and abscess formation at the site of injection of antibiotics in the buttock.

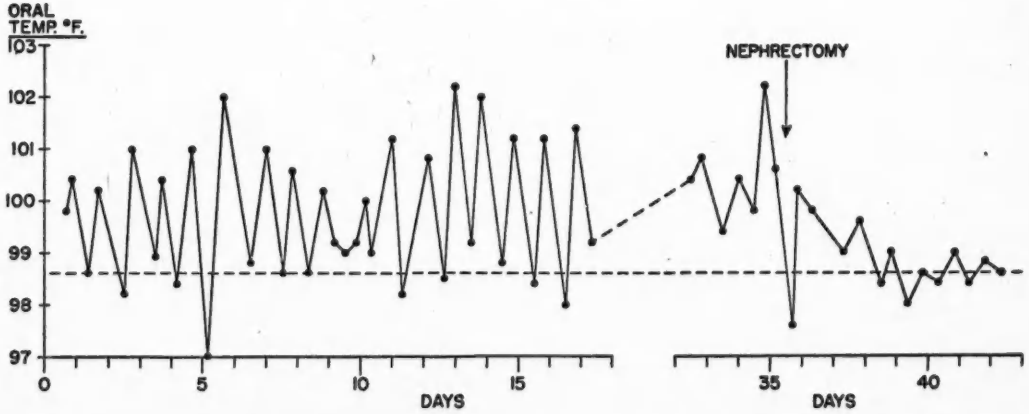

FIG. 9.—A portion of the temperature record of a patient who had fever for 16 months showing prompt defervescence after surgical removal of a hypernephroma.

underwent cholecystectomy and exploration of the common bile duct. She became febrile postoperatively despite "routine antibiotic prophylaxis" in the form of streptomycin and penicillin and suffered a series of mishaps that included blockage of the T tube that had been left in the common duct, dehiscence of the operative wound and ileus, necessitating nasogastric and rectal intubation and parenteral alimentation. When seen by a medical consultant on the 30th hospital day, there were tubes in several orifices and she was receiving an intravenous infusion. In the absence of physical findings suggesting pneumonia, wound infection or thrombophlebitis, the consultant suggested that antibiotics be discontinued in view of the possibility of drug fever. This procedure failed to modify the patient's course. Several days later, the cause of the fever was found to be a large gluteal abscess at the site of injections of the "prophylactic antibiotics." Dramatic defervescence and prompt recovery followed incision and drainage. Culture of the pus grew resistant Proteus, staphylococcus and enterococcus, an excellent demonstration of the fallacy of trying to prevent infection in this type of situation with antibiotics. Review of the case revealed that the presence of a large, tender, reddened swelling in the buttock had been known to the ward nurses for at least 2 weeks, having been noted by them when the patient was turned to receive injections. The lesion had escaped detection by surgeon and medical consultant, neither of whom had turned the patient for fear of disturbing the elaborate maze of tubes. The nursing staff had not mentioned the gluteal mass because they had been sure that its presence was known. After all, she was being seen daily by both the surgeon and the consulting physician! This case illustrates the fact that a *patient is never too sick to be examined.*

Figure 9 depicts a portion of the temperature chart of a 55-year-old woman hospitalized because of daily fever of 101-103 F. for 16 months. There had been occasional shaking chills and a weight loss of 25 pounds. Her only complaint was fatigability. Her father, sister, uncle and aunt had all died of tuberculosis and she had been hospitalized for 3 years for pulmonary tuberculosis discovered at the age of 29. There had been no roentgenologic or other evidence of activity of the tuberculous process for more than 20 years. During the course of the prolonged fever, she had been studied extensively in several medical centers with myriads of cultures, serologic tests, x-rays, biopsies of bone marrow and liver, a therapeutic trial of streptomycin and

chlortetracycline for brucellosis and a trial of chloroquine for malaria or hepatic amebiasis. She had taken prednisone for a period of 3 months with decrease in fever but prompt recurrence when the hormone was discontinued. At the time of the hospitalization, there was evidence of weight loss and both kidneys were

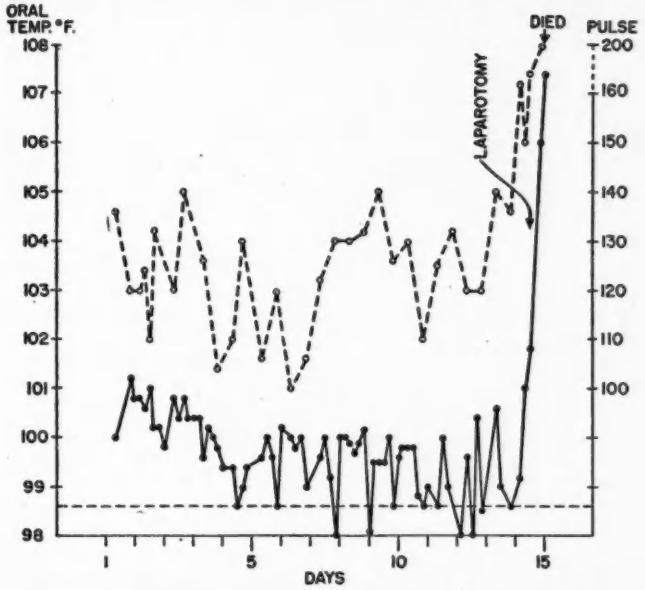

FIG. 10.—Fatal thyrotoxic crisis induced by exploratory laparotomy in a patient with previously unrecognized hyperthyroidism. The dotted line is the pulse-rate and the solid line the temperature.

easily palpable, the left being slightly tender. There were no other findings. X-ray of the chest showed linear and nodular densities extending from the hila to the apices bilaterally. She was not anemic, urinalysis was normal and cultures, serologic tests and blood chemical examinations were unrevealing. Tubercle bacilli were not found in smears or cultures of gastric washings and urine. Intravenous pyelograms were interpreted as normal but disagreement arose among the attending physicians

about the possibility of slight derangement of the calyceal system on the left. The resulting discussion led to a repetition of pyelography with tomography of the left kidney area. This procedure revealed enough irregularity of the left renal shadow to prompt an exploratory operation, at which time nephrectomy was carried out for removal of a tumor measuring 5×8×11 cm.

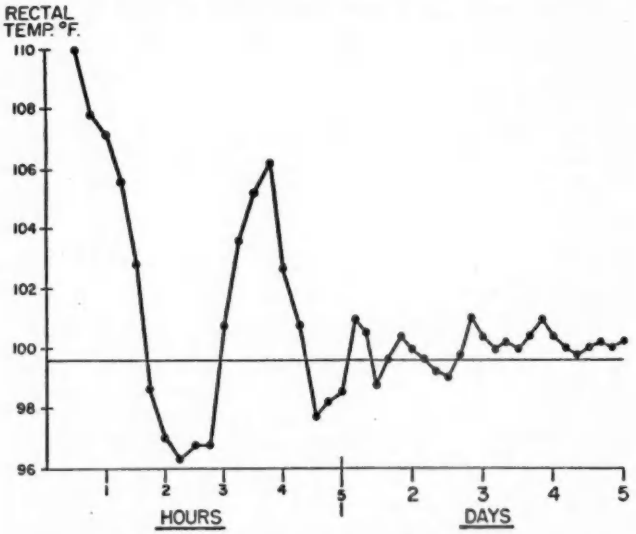

FIG. 11.—Rapid fluctuation in rectal temperature of patient rendered poikilothermic by heat stroke. Initial hyperthermia gave way to hypothermia when the patient was sponged with ice water and rewarming with blankets was followed by recurrence of fever, requiring additional sponging.

Histologic sections were typical of hypernephroma. Defervescence was prompt and she was well and afebrile when last seen, 7 months postoperatively. In summary, hypernephroma produced daily fever for 16 months in this patient; prednisone decreased the fever temporarily. Diagnosis was delayed by a past history of tuberculosis, extensive fibrocalcific changes in the lungs and equivocal findings on pyelography despite the large size of the tumor.

Figure 10 illustrates the pulse and temperature record of a patient hospitalized in 1940 for abdominal pain and low-grade fever. She showed tachycardia out of proportion to the fever, but the significance of this was not immediately appreciated since attention centered on the possibility of abdominal disease. She underwent abdominal exploration which revealed no abnormality. Postoperatively she developed striking tachycardia, dyspnea, hyperthermia and delirium—a typical thyroid storm. Despite intensive measures to combat hyperthermia, she succumbed rapidly. This patient's abdominal pain led to operation in the presence of unrecognized hyperthyroidism with precipitation of a fatal thyrotoxic crisis.

Figure 11 is the record of rectal temperature in a patient with heat stroke. He was unconscious with a blood pressure of 50/0 and a rectal temperature of 110 F. The skin was flushed, hot and dry. Sponging with ice water produced a drop in body temperature to hypothermic levels necessitating the application of blankets. This procedure was immediately followed by recurrence of fever requiring additional sponging. He remained disoriented for 48 hours but heat regulation returned to normal and he was discharged asymptomatic several days later. The patient's platelet count was 49,000/mm^3 when admitted and multiple petechiae appeared at the sites of vigorous sponging. The thrombocytopenia disappeared gradually during the next 6 days. This is a common finding with heat stroke, and petechiae may be numerous when patients are first seen. This case not only demonstrates the hyperthermia that can accompany heat stroke, but also the total loss of heat control and poikilothermia that makes body temperature in these patients as dependent on external conditions as it is in premature infants. This cycle of hyperthermia and hypothermia is not at all unusual and it requires some skill to get these patients in balance. With recovery, there is rapid re-establishment of body heat control.

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